Capsule

Genome-wide association study indicates two novel resistance loci for severe malaria

Malaria causes approximately one million fatalities per year, mostly among African children. Although highlighted by the strong protective effect of the sickle-cell trait, the full impact of human genetics on resistance to the disease remains largely unexplored. Genome-wide association (GWA) studies are designed to unravel relevant genetic variants comprehensively; however, in malaria, as in other infectious diseases, these studies have been only partly successful. Timmann et al. identified two previously unknown loci associated with severe falciparum malaria in patients and controls from Ghana, West Africa. They applied the GWA approach to the diverse clinical syndromes of severe falciparum malaria, thereby targeting human genetic variants influencing any step in the complex pathogenesis of the disease. One of the loci was identified on chromosome 1q32 within the *ATP2B4* gene, which encodes the main calcium pump of erythrocytes, the host cells of the pathogenic stage of malaria parasites. The second was indicated by an intergenic single nucleotide polymorphism on chromosome 16q22.2, possibly linked to a neighboring gene encoding the tight-junction protein MARVELD3. The protein is expressed on endothelial cells and might therefore have a role in microvascular damage caused by endothelial adherence of parasitized erythrocytes. They also confirmed previous reports on protective effects of the sickle-cell trait and blood group O. Their findings underline the potential of the GWA approach to provide candidates for the development of control measures against infectious diseases in humans.

Nature 2012; 489: 443

Eitan Israeli

Capsule

Germline mutations account for susceptibility to tuberculosis vaccine

Some children experience severe clinical disease when they are vaccinated against tuberculosis, an attenuated live vaccine that is normally innocuous in humans. Several germline mutations have been identified that account for this susceptibility, and now Bogunovic et al. add another to the list – ISG15. Uncovering this mutation, which is inherited in an autosomal recessive manner, was a surprise because studies with mice deficient in ISG15 showed enhanced susceptibility to some viral, but not bacterial, infections. Nevertheless, patients lacking ISG15 were not able to produce adequate amounts of interferon-gamma, a cytokine critical for clearance of the bacteria.

Science 2012; 337: 1684

Eitan Israeli

Capsule

Human ES-cell-derived cardiomyocytes electrically couple and suppress arrhythmias in injured hearts

Transplantation studies in mice and rats have shown that human embryonic stem cell-derived cardiomyocytes (hESC-CMs) can improve the function of infarcted hearts, but two critical issues related to their electrophysiological behavior in vivo remain unresolved. First, the risk of arrhythmias following hESC-CM transplantation in injured hearts has not been determined. Second, the electromechanical integration of hESC-CMs in injured hearts has not been demonstrated, so it is unclear whether these cells improve contractile function directly through addition of new force-generating units. Shiba and team used a guinea-pig model to show that hESC-CM grafts in injured hearts protect against arrhythmias and can contract synchronously with host muscle. Injured hearts with hESC-CM grafts showed improved mechanical function and a significantly reduced incidence of both spontaneous and induced ventricular tachycardia. To assess the activity of hESC-CM grafts in vivo, the authors transplanted hESC-CMs expressing the genetically encoded calcium sensor, GCaMP3. By correlating the GCaMP3 fluorescent signal with the host ECG, they found that grafts in uninjured hearts had consistent 1:1 host–graft coupling. Grafts in injured hearts were more heterogeneous and typically included both coupled and uncoupled regions. Thus, human myocardial grafts met physiological criteria for true heart regeneration, providing support for the continued development of hESC-based cardiac therapies for both mechanical and electrical repair.

Nature 2012; 489: 322

Eitan Israeli

Capsule

Infection induced NETosis is a dynamic process involving neutrophil multitasking in vivo

Neutrophil extracellular traps (NETs) are released as neutrophils die in vitro in a process requiring hours, leaving a temporal gap that invasive microbes may exploit. Neutrophils capable of migration and phagocytosis while undergoing NETosis have not been documented. During Gram-positive skin infections, Yipp et al. directly visualized live polymorphonuclear cells (PMNs) in vivo, rapidly releasing NETs, which prevented systemic bacterial dissemination. NETosis occurred during crawling, thereby casting large areas of NETs. NET-releasing PMNs developed diffuse decondensed nuclei, ultimately becoming devoid of DNA. Cells with abnormal nuclei showed unusual crawling behavior highlighted by erratic pseudopods and hyperpolarization consistent with the nucleus being a fulcrum for crawling. A requirement for both Toll-like receptor 2 and complement-mediated opsonization tightly regulated NET release. Additionally, live human PMNs injected into mouse skin developed decondensed nuclei and formed NETS in vivo, and intact anuclear neutrophils were abundant in Gram-positive human abscesses. Therefore early in infection NETosis involves neutrophils that do not undergo lysis and retain the ability to multitask.

Nature Med 2012; 18: 1386

Eitan Israeli

Capsule

Rinderpest eradication: appropriate technology and social innovations

Acquired resistance to anticancer treatments is a substantial barrier to reducing the morbidity and mortality that is attributable to malignant tumors. Components of tissue microenvironments are recognized to profoundly influence cellular phenotypes, including susceptibilities to toxic insults. Using a genome-wide analysis of transcriptional responses to genotoxic stress induced by cancer therapeutics, Sun and co-authors identified a spectrum of secreted proteins derived from the tumor microenvironment that includes the Wnt family member wingless-type MMTV integration site family member 16B (WNT16B). The authors determined that WNT16B expression is regulated by nuclear factor of κ light polypeptide gene enhancer in B cells 1 (NF-κB) after DNA damage and subsequently signals in a paracrine manner to activate the canonical Wnt program in tumor cells. The expression of WNT16B in the prostate tumor microenvironment attenuated the effects of cytotoxic chemotherapy in vivo, promoting tumor cell survival and disease progression. These results delineate a mechanism by which genotoxic therapies given in a cyclical manner can enhance subsequent treatment resistance through cell non-autonomous effects that are contributed by the tumor microenvironment.

Nature Med 2012; 18: 1359

Eitan Israeli

Capsule

Comprehensive molecular portraits of human breast tumors

The Cancer Genome Atlas Network analyzed primary breast cancers by genomic DNA copy number arrays, DNA methylation, exome sequencing, messenger RNA arrays, microRNA sequencing and reverse-phase protein arrays. The ability to integrate information across platforms provided key insights into previously defined gene expression subtypes and demonstrated the existence of four main breast cancer classes when combining data from five platforms, each of which shows significant molecular heterogeneity. Somatic mutations in only three genes (*TP53*, *PIK3CA* and *GATA3*) occurred at › 10% incidence across all breast cancers; however, there were numerous subtype-associated and novel gene mutations including the enrichment of specific mutations in *GATA3*, *PIK3CA* and *MAP3K1* with the luminal A subtype. The team identified two novel protein expression-defined subgroups, possibly produced by stromal/microenvironmental elements, and integrated analyses identified specific signaling pathways dominant in each molecular subtype including a HER2/phosphorylated HER2/EGFR/phosphorylated EGFR signature within the HER2-enriched expression subtype. Comparison of basal-like breast tumors with high-grade serous ovarian tumors showed many molecular commonalities, indicating a related etiology and similar therapeutic opportunities. The biological finding of the four main breast cancer subtypes caused by different subsets of genetic and epigenetic abnormalities raises the hypothesis that much of the clinically observable plasticity and heterogeneity occurs within, and not across, these major biological subtypes of breast cancer.

Nature 2012; 490: 61

Eitan Israeli

Capsule

A metagenome-wide association study of gut microbiota in type 2 diabetes

Assessment and characterization of gut microbiota has become a major research area in human disease, including type 2 diabetes, the most prevalent endocrine disease worldwide. To carry out analysis on gut microbial content in patients with type 2 diabetes, Qin et al. developed a protocol for a metagenome-wide association study (MGWAS) and undertook a two-stage MGWAS based on deep shotgun sequencing of the gut microbial DNA from 345 Chinese individuals. The authors identified and validated approximately 60,000 type 2 diabetes-associated markers and established the concept of a metagenomic linkage group, enabling taxonomic species-level analyses. MGWAS analysis showed that patients with type 2 diabetes were characterized by a moderate degree of gut microbial dysbiosis, a decrease in the abundance of some universal butyrate-producing bacteria, and an increase in various opportunistic pathogens, as well as an enrichment of other microbial functions conferring sulphate reduction and oxidative stress resistance. An analysis of 23 additional individuals demonstrated that these gut microbial markers might be useful for classifying type 2 diabetes.

Nature 2012; 490: 55

Eitan Israeli

Capsule

An atlas of Epstein-Barr virus

Epstein-Barr virus (EBV), which has been associated with B cell lymphomas, gastic carcinomas, and nasopharyngeal carcinoma, may be responsible for 1% of all human cancers. Arvey and co-workers have pooled data from nucleosome positioning maps and viral protein-binding analyses with more than 700 publicly available high-throughput sequencing data sets from human lymphoblastoid cell lines to generate a large-scale functional genomics atlas of the virus. Although much of the data were already publicly available, it was scattered, and has now been integrated in a highly usable form. Their analysis revealed possible regulatory domains within the viral genome and combinatorial control of viral gene expression by human transcription factors. There were also indications of three-dimensional organization, including loop formation between the viral origin of latent replication and latent membrane proteins 1 and 2, linked by human transcriptional repressor CTCF and cohesin. B cell specificity factor Pax5 was shown to bind to EBV terminal repeats, and depletion experiments showed that Pax5 is involved in the regulation of EBV transcription during latent infection.

Cell Host Microbe 2012; 12: 233

Eitan Israeli

Capsule

Structural and genetic basis for development of broadly neutralizing influenza antibodies

Influenza viruses take a yearly toll on human life despite efforts to contain them with seasonal vaccines. These viruses evade human immunity through the evolution of variants that resist neutralization. The identification of antibodies that recognize invariant structures on the influenza hemagglutinin (HA) protein have invigorated efforts to develop universal influenza vaccines. Specifically, antibodies to the highly conserved stem region of HA neutralize diverse viral subtypes. These antibodies largely derive from a specific antibody gene, heavy chain variable region *IGHV1-69*, after limited affinity maturation from their germline ancestors, but how HA stimulates naive B cells to mature and induce protective immunity is unknown. To address this question, Lingwood and team analyzed the structural and genetic basis for their engagement and maturation into broadly neutralizing antibodies. The authors show that the germline-encoded precursors of these antibodies act as functional B cell antigen receptors (BCRs) that initiate subsequent affinity maturation. Neither the germline precursor of a prototypic antibody, CR6261, nor those of two other natural human IGHV1-69 antibodies, bound HA as soluble immunoglobulin-G (IgG). However, all three IGHV1-69 precursors engaged HA when the antibody was expressed as cell surface IgM. HA triggered BCR-associated tyrosine kinase signaling by germline transmembrane IgM. Recognition and virus neutralization was dependent solely on the heavy chain, and affinity maturation of CR6261 required only seven amino acids in the complementarity-determining region (CDR) H1 and framework region 3 (FR3) to restore full activity. These findings provide insight into the initial events that lead to the generation of broadly neutralizing antibodies to influenza, informing the rational design of vaccines to elicit such antibodies and providing a model relevant to other infectious diseases, including human immunodeficiency virus/AIDS. The data further suggest that selected immunoglobulin genes recognize specific protein structural 'patterns' that provide a substrate for further affinity maturation.

Nature 2012; 489: 566

Eitan Israeli

Capsule

Type I interferon induces necroptosis in macrophages during infection with *Salmonella enterica* serovar Typhimurium

Salmonella enterica serovar Typhimurium (*S. typhimurium*) is a virulent pathogen that induces rapid host death. Robinson et al. observed that host survival after infection with *S. typhimurium* was enhanced in the absence of type I interferon signaling, with improved survival of mice deficient in the receptor for type I interferons (*Ifnar1*−/− mice) that was attributed to macrophages. Although there was no impairment in cytokine expression or inflammasome activation in *Ifnar1*−/− macrophages, they were highly resistant to *S. typhimurium*-induced cell death. Specific inhibition of the kinase RIP1 or knockdown of the gene encoding the kinase RIP3 prevented the death of wild-type macrophages, which indicated that necroptosis was a mechanism of cell death. Finally, RIP3-deficient macrophages, which cannot undergo necroptosis, had similarly less death and enhanced control of *S. typhimurium* in vivo. Thus, we propose that *S. typhimurium* induces the production of type I interferon, which drives necroptosis of macrophages and allows them to evade the immune response.

Nature Immunol 2012; 13: 954

Eitan Israeli

Capsule

Comprehensive genomic characterization of squamous cell lung cancers

Lung squamous cell carcinoma is a common type of lung cancer, causing approximately 400,000 deaths per year worldwide. Genomic alterations in squamous cell lung cancers have not been comprehensively characterized, and no molecularly targeted agents have been specifically developed for its treatment. As part of The Cancer Genome Atlas, the team profiles 178 lung squamous cell carcinomas to provide a comprehensive landscape of genomic and epigenomic alterations. They show that the tumor type is characterized by complex genomic alterations, with a mean of 360 exonic mutations, 165 genomic rearrangements, and 323 segments of copy number alteration per tumor. They find statistically recurrent mutations in 11 genes, including mutation of *TP53* in nearly all specimens. Previously unreported loss-of-function mutations are seen in the *HLA-A* class I major histocompatibility gene. Significantly altered pathways included *NFE2L2* and *KEAP1* in 34%, squamous differentiation genes in 44%, phosphatidylinositol-3-OH kinase pathway genes in 47%, and *CDKN2A* and *RB1* in 72% of tumors. We identified a potential therapeutic target in most tumors, offering new avenues of investigation for the treatment of squamous cell lung cancers.

Nature 2012; 489: 519

Eitan Israeli

Capsule

Induction and molecular signature of pathogenic T_H17 cells

Interleukin 17 (IL-17)-producing helper T cells (T_H17 cells) are often present at the sites of tissue inflammation in autoimmune diseases, which has led to the conclusion that T_H17 cells are main drivers of autoimmune tissue injury. However, not all T_H17 cells are pathogenic; in fact, T_H17 cells generated with transforming growth factor-β1 (TGF-β1) and IL-6 produce IL-17 but do not readily induce autoimmune disease without further exposure to IL-23. Lee et al. found that the production of TGF-β3 by developing T_H17 cells was dependent on IL-23, which together with IL-6 induced very pathogenic T_H17 cells. Moreover, TGF-β3-induced T_H17 cells were functionally and molecularly distinct from TGF-β1-induced T_H17 cells and had a molecular signature that defined pathogenic effector T_H17 cells in autoimmune disease.

*Nature Immun*ol 2012; 13: 991

Eitan Israeli

Capsule

Pregnancy imprints regulatory memory that sustains anergy to fetal antigen

Pregnancy is an intricately orchestrated process where immune effector cells with fetal specificity are selectively silenced. This requires the sustained expansion of immune-suppressive maternal FOXP3+ regulatory T cells (Treg cells), because even transient partial ablation triggers fetal-specific effector T cell activation and pregnancy loss. In turn, many idiopathic pregnancy complications proposed to originate from disrupted fetal tolerance are associated with blunted maternal Treg expansion. Importantly, however, the antigen specificity and cellular origin of maternal Treg cells that accumulate during gestation remain incompletely defined. Rowe et al. show that pregnancy selectively stimulates the accumulation of maternal FOXP3+ CD4 cells with fetal specificity using tetramer-based enrichment that allows the identification of rare endogenous T cells. Interestingly, after delivery, fetal-specific Treg cells persist at elevated levels, maintain tolerance to pre-existing fetal antigen, and rapidly re-accumulate during subsequent pregnancies. The accelerated expansion of Treg cells during a secondary pregnancy was driven almost exclusively by proliferation of fetal-specific FOXP3+ cells retained from a prior pregnancy, whereas induced FOXP3 expression and proliferation of pre-existing FOXP3+ cells each contribute to Treg expansion during the primary pregnancy. Furthermore, fetal resorption in secondary compared with primary pregnancy becomes more resilient to partial maternal FOXP3+ cell ablation. Thus, pregnancy imprints FOXP3+ CD4 cells that sustain protective regulatory memory to fetal antigen. We anticipate that these findings will spark further investigation on maternal regulatory T cell specificity that unlocks new strategies for improving pregnancy outcomes and novel approaches for therapeutically exploiting Treg cell memory.

Nature 2012; 490: 102

Eitan Israeli

Capsule

The immune system keeps cancer cells at bay

Cancer cells are often aneuploid; that is, they have an abnormal number of chromosomes. But to what extent this contributes to the tumorigenic phenotype is not clear. Senovilla et al. found that tetraploidization of cancer cells can cause them to become immunogenic and thus aid in their clearance from the body by the immune system. Cells with excess chromosomes put stress on the endoplasmic reticulum, which leads to movement of the protein calreticulin to the cell surface. Calreticulin exposure in turn caused recognition of cancer cells in mice by the host immune system. Thus, the immune system appears to serve a protective role in eliminating hyperploid cells that must be overcome to allow unrestricted growth of cancer cells.

Science 2012; 337: 1678

Eitan Israeli

Capsule

Essential neuroanatomical substrates of some of the highest brain functions

Although the human brain's prefrontal cortex (PFC) has been studied for decades, theories about a valuation network and a cognitive control network – both hypothesized to reside in the PFC – have only recently emerged, and their precise distinction is still unclear. Furthermore, cognitive control, once considered a unitary construct, is now thought to fractionate into distinct executive functions whose neural correlates remain elusive. It is thus still an unanswered question how these processes map onto distinct or possibly overlapping sectors of the PFC. Glaescher and co-researchers applied several new statistical mapping approaches to a sample of 344 lesion patients that had received an array of neuropsychological tests of executive functions and value-based decision-making. Background data regarding IQ, memory, and other cognitive functions within individual subjects were also analyzed. The authors described detailed maps of PFC regions that are essential for different executive functions. One set involving the dorsolateral PFC and the anterior cingulate cortex is associated with a common performance factor related to flexibly switching between task and response sets, a hallmark of cognitive control. Another set involving the orbitofrontal cortex, ventromedial PFC, and frontopolar cortex is involved in value-based decision-making. This study details the essential neuroanatomical substrates of some of the highest brain functions and provides insights about the extent to which they are distinct or overlap.

Proc Natl Acad Sci USA 2012; 109: 14681

Eitan Israeli

Capsule

Cross-neutralization of influenza A viruses mediated by a single antibody loop

Immune recognition of protein antigens relies on the combined interaction of multiple antibody loops, which provide a fairly large footprint and constrain the size and shape of protein surfaces that can be targeted. Single protein loops can mediate extremely high affinity binding, but it is unclear whether such a mechanism is available to antibodies. Ekiert et al. report the isolation and characterization of an antibody called C05, which neutralizes strains from multiple subtypes of influenza A virus, including H1, H2 and H3. X-ray and electron microscopy structures show that C05 recognizes conserved elements of the receptor-binding site on the hemagglutinin surface glycoprotein. Recognition of the hemagglutinin receptor-binding site is dominated by a single heavy chain complementarity-determining region 3 loop, with minor contacts from heavy chain complementarity-determining region 1, and is sufficient to achieve nanomolar binding with a minimal footprint. Thus, binding predominantly with a single loop can allow antibodies to target small, conserved functional sites on otherwise hypervariable antigens.

Nature 2012; 489: 526

Eitan Israeli